Increased homocarnosine is associated with improved seizure control.

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Introduction. Homocarnosine, a dipeptide of gamma-aminobutyric acid (GABA) and histidine, is thought to be an inhibitory neuromodulator synthesized in subclasses of GABAergic neurons. Homocarnosine immunoreactivity is seen along projecting fibers into the neocortex Homocarnosinase, the specific degradative enzyme, is associated with synapses of projecting fibers with an extracellular location. Hydrolysis of homocarnosine has been proposed as an alternate metabolic pathway to rapidly increase GABAergic activity [1]. Homocarnosine is present in human brain in greater amounts (0.4 - 1.0 μmol/g) than in other mammals [2]. In humans, total CSF GABA consists of micromolar concentrations of homocarnosine and 2-pyrrolidinone (the internal lactam of GABA), small amounts of other GABA containing peptides, and nanomolar quantities of free GABA [3].

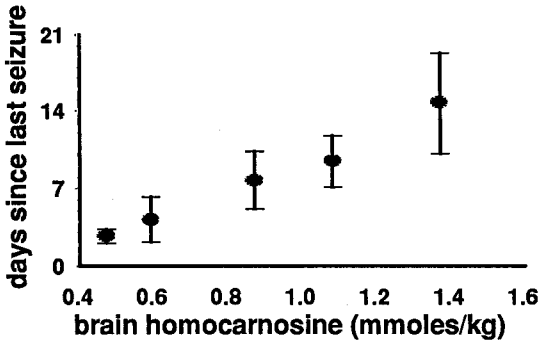
Vigabatrin is a potent new antiepileptic drug designed to increase brain GABA by irreversibly inhibiting GABA transaminase [4, 5]. Homocarnosine levels rise in human CSF in proportion to vigabatrin dose and correlate with improved seizure control. The relationship between free GABA concentration and seizure control is less clear [6].

Methods. Studies were done with a 2.1 Tesla Oxford Magnet Technologies 1 meter bore magnet equipped with an extensively modified Biospec I spectrometer and OMT shielded gradients and power supplies. The back of the head rested on an 8 cm distributed capacitance radio-frequency surface coil tuned to the ^{1}H NMR frequency of 89.43 MHz. From the scout image a 1.5x3.0x3.0 cm (14 cm^3) volume in the occipital cortex was chosen. Localized homocarnosine measurements were performed using short TE spectra with and without the "metabolite nulled" inversion recovery sequence [7, 8]. Subtracting signals from macromolecule resonances results in a flat baseline. Homonuclear editing of the 3.0 ppm C4 GABA resonance was performed using the J-editing pulse sequence described previously [9, 10]. A brain creatine concentration of 9 μmol/g brain was used as a standard [11].

Results and Discussion. Nineteen patients with complex partial epilepsy treated with vigabatrin and eleven seizure free, drug free control subjects were studied. Prior to each measurement patients were asked when their last seizure occurred. Serial spectra show that occipital lobe homocarnosine levels increased with the addition of vigabatrin to other antiepileptic medications. The most intense resonance at 7.9 ppm has was assigned to the amide group of N-acetylaspartate. The difference spectra revealed two resonances at 7.05 and 8.02 ppm assigned to the histadyl protons primarily from homocarnosine.

Before vigabatrin, occipital lobe homocarnosine concentrations were 0.47 μmol/g (sd 0.24, n 11), indistinguishable from normal (0.46 μmol/g, sd 0.14, n 11). With low dose daily vigabatrin (1-2 g) homocarnosine rose to 0.88 μmol/g (sd 0.29, n 11). On standard dose vigabatrin (3-4 g), homocarnosine rose further to 1.17 μmol/g (se 0.26, n 14). High dose vigabatrin (5-6 g daily)failed to increase homocarnosine further (1.08 μmol/g, sd 0.21, n 18).

Editing measurements performed on a homocarnosine phantom indicate that at 3.0 ppm homocarnosine co-edits with C4 GABA with the same editing efficiency [8]. Subtracting homocarnosine from edited GABA yield an estimate of the GABA concentration. Possible contributions from other dipeptides such a GABA-lysine (0.05 μmol/g) are negligible [2]. Before vigabatrin, GABA levels were slightly lower in patients (0.56 μmol/g, sd 0.34, n 11) than in controls (0.72 μmol/g, sd 0.17, n 11). Low dose vigabatrin (1-2 g) increased GABA to 0.95 μmol/g (sd 0.36, n 11). Brain GABA did not increase further with standard dose (0.97 μmol/g (sd 0.39, n 14) or high dose vigabatrin (1.11 μmol/g, sd 0.32, n 18). Inhibition of GABA-transaminase by vigabatrin thereby increasing GABA activates alternative pathways of GABA metabolism.



The graph plots mean (se) days without seizure as a function of brain homocarnosine. Seizure control improved more than 50% with above normal homocarnosine levels in most patients. Increased homocarnosine failed to benefit some patients. With homocarnosine levels of 0.7-1.0 μmol/g, 27% of patients improved; at 1.0-1.2 μmol/g, 57% improved; with homocarnosine above 1.2 μmol/g, 69% improved.

Increased total GABA concentrations in human CSF and brain correlate well with improved seizure control during vigabatrin therapy, reflecting an increase in GABA and homocarnosine [10, 12]. With low doses of vigabatrin, the primary effect appears to be an increase in GABA. At standard doses, homocarnosine increased with minimal change in GABA. Neither increased further at high doses. The increase in homocarnosine correlated with improved seizure control.

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